Studies on the Reaction Between Chloral and Alcohols

X. Investigations on the Anomalous Mutarotation of Chloral Hemiacetals of Optically Active Secondary Alcohols

ROALD BOE JENSEN, SØREN BOLS PEDERSEN and
BODIL HESSELBJERG

Chemical Laboratory II (General and Organic Chemistry), University of Copenhagen,
The H. C. Ørsted Institute, DK-2100 Copenhagen, Denmark

The course of the mutarotation (due to epimerization) of chloral hemiacetals of a large number of optically active secondary alcohols containing polar radicals such as $COOR$, CH_2COOR, C_6H_5, $C_6H_5CH_2$, $CH_2=CH$, $CH_2=CHCH_2$, trans-$CH_3CH=CH$, and Br is followed by UV- and ^1H NMR-spectroscopy. For most of these alcohols the slope of the last part of the mutarotation curves is opposite to that predicted on the basis of the steric requirements of the groups surrounding the hydroxyl substituted chiral carbon atom. As reported earlier such predictions are possible for alcohols containing nonpolar radicals.

As noted earlier the observed mutarotation was found to consist of a catalyzed and an uncatalyzed mutarotation. In this paper it is shown that the directions of these mutarotations are the same whether the alcohol used contains polar groups or not.

Further the conditions for obtaining an observable mutarotation for hemiacetals of optically active alcohols of the following types,

$$CH_3(CH_2)_m\overset{*}{C}HOH(CH_2)_nCH_3 \quad \text{and} \quad CH_3CH_2\overset{*}{C}H(CH_3)(CH_2)_nOH,$$

are discussed, and in connection with these considerations the validity of the van't Hoff rule of superposition has been examined.

Finally acetylation of a solution of the 2-butanol hemiacetal of chloral yields two components which can be separated by gas chromatography.
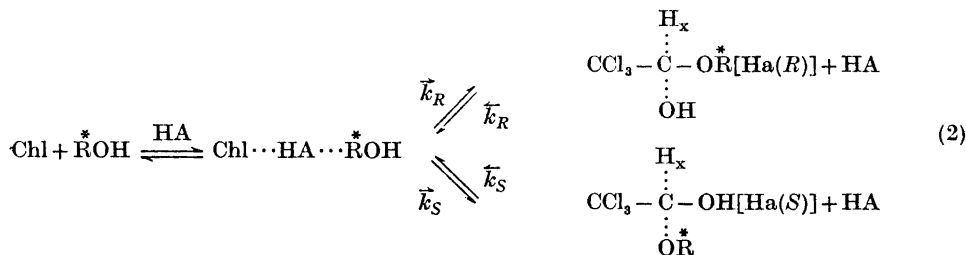
GENERAL SCOPE OF EPIMERIZATION

In previous papers [1-4,14] we have reported that chloral hemiacetals made from chloral and optically active alcohols of the following type underwent mutarotation in hydrocarbon and methylene chloride solutions (1).

$$
\begin{array}{c}
M \\
\vdots \\
L - \overset{*}{C} - (CH_2)_nOH \\
\vdots \\
S
\end{array}
\qquad (1)
$$

L, M, and S mean large, medium and small with respect to steric bulk.

The rate of the mutarotation was found to be accelerated by the presence of small amounts of acetic acid. The mutarotation was explained as an equilibrium asymmetric transformation [6] (epimerization) of one of the two possible diastereomeric hemiacetals Ha(R) and Ha(S), into the other (2).

$$
Chl + \overset{*}{R}OH \xrightleftharpoons{HA} Chl \cdots HA \cdots \overset{*}{R}OH
\begin{array}{c}
\overset{\overleftarrow{k_R}}{\underset{\overrightarrow{k_R}}{\nearrow}} \\
\overset{\overrightarrow{k_S}}{\underset{\overleftarrow{k_S}}{\searrow}}
\end{array}
\begin{array}{c}
H_x \\
CCl_3 - \overset{|}{\underset{|}{C}} - O\overset{*}{R}[Ha(R)] + HA \\
OH \\
\\
H_x \\
CCl_3 - \overset{|}{\underset{|}{C}} - OH[Ha(S)] + HA \\
O\overset{*}{R}
\end{array}
\tag{2}
$$

$\overrightarrow{k_R}$ and $\overrightarrow{k_S}$ are rate-constants for the formation of Ha(R) and Ha(S).
$\overleftarrow{k_R}$ and $\overleftarrow{k_S}$ » » » » dissociation of Ha(R) and Ha(S).

The mutarotation was described by the change in molecular rotation of the hemiacetal mixture, $[\phi_{Ha}]$, with time, t. The process of epimerization occurs when a non-equilibrium mixture, such as a mixture of Ha(R) and Ha(S), initially formed by kinetic control undergoes equilibration. The condition for epimerization is that the difference in free energy of activation, $\Delta G_{Ha(R)}^{\ddagger} - \Delta G_{Ha(S)}^{\ddagger}$, is different from the difference in free energy of formation, $\Delta G_{Ha(R)} - \Delta G_{Ha(S)}$, of Ha($R$) and Ha($S$). This leads to the following inequality, where the equilibrium constants $K_{Ha(R)}$ and $K_{Ha(S)}$ equal $\overrightarrow{k_R}/\overleftarrow{k_R}$ and $\overrightarrow{k_S}/\overleftarrow{k_S}$, respectively (3).

$$
\frac{K_{Ha(R)}}{K_{Ha(S)}} \neq \frac{\overrightarrow{k}_{Ha(R)}}{\overrightarrow{k}_{Ha(S)}}
\tag{3}
$$

In order to visualize the conditions necessary to cause epimerization some energy profiles are presented in Figs. 1a, b, c, and d. Figs. 1a, b, and c illustrate cases where epimerization will occur. In contrast, this is not the case for Fig. 1d, where no epimerization will occur because eqn. (3) is not valid.

That the mutarotation should be due to the occurrence of epimerization was supported by the following observations.

(a) A plot of log ($[\phi_{Ha}]_t - [\phi_{Ha}]_\infty$) versus time, where $[\phi_{Ha}]_t$ and $[\phi_{Ha}]_\infty$ are molecular rotations of the hemiacetal mixture at time t and at equilibrium, respectively, gave a straight line;[1] a similar relationship has been observed by Hudson [7] for the isomerization of α- and β-glucose.

(b) The sign of $d[\phi_{Ha}]/dt$ was found to be related to the spatial arrangement of the groups L, M, S, and $(CH_2)_n$ OH surrounding the asymmetric carbon atom in the optically active alcohol shown in (1). It was shown that a negative value of $d[\phi_{Ha}]/dt$ corresponds to a right-handed sequence of L, M, and S (noted as L → M → S when L, M, and S follow a clockwise sequence when viewed from the asymmetric carbon atom) and a positive value of $d[\phi_{Ha}]/dt$ corresponds to a left-handed sequence.
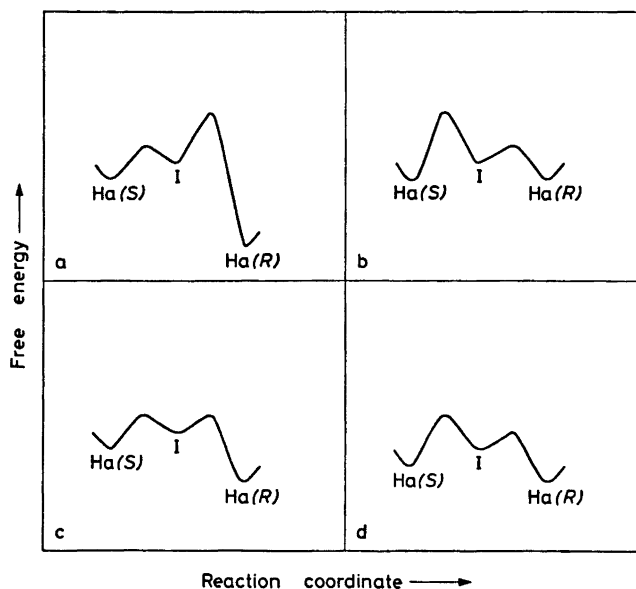
Fig. 1a, b, c, and d. Energy profiles illustrating the conditions for epimerization. I refers to the common reaction complex Chl···HA···ROH from which the two diastereomeric chloral hemiacetal Ha(R) and Ha(S) are formed.

It is important to remember that the sequence rule in this case does not have to be synonymous with the absolute configuration in terms of (R,S)-nomenclature and *vice versa*. The general idea of absolute configurations refers only to the geometrical arrangement in space of the groups surrounding the asymmetric center and not to their function as a controlling factor in an asymmetric reaction. It is necessary to determine experimentally a priority rule for the various groups surrounding the asymmetric center for every new type of asymmetric reaction. In our case, as is the case with most asymmetric reactions, it seems that the asymmetric activity of an alkyl group is due only to steric effects (4).

$$H < CH_3 < CH_3CH_2 < CH_3(CH_2)_nCH_2 < (CH_3)_2CHCH_2 < (CH_3)_2CH < (CH_3)_3C \qquad (4)$$

This also corresponds to the observations made by McKenzie,[8] Prelog,[9] Ingold,[10] Cram,[11] and others.[12]

Van't Hoff's rule of optical superposition, discussed by Eliel,[13] concludes that: "Like functional groups in like surroundings make like contributions to the optical rotation." This means that the molecular rotation of the diastereomeric hemiacetals, $[\phi_{Ha(R)}]$ and $[\phi_{Ha(S)}]$, of optically active alcohols can be made up by a contribution from the active center(s) in the ROH component, $[\phi_{ROH}]$, and of a contribution from the created asymmetric center in the chloral moiety of the hemiacetal, $[\phi_{Chl}]$ (5).

$$[\phi_{Ha(R)}] = [\phi_{ROH}] + [\phi_{Chl}] \quad \text{and} \quad [\phi_{Ha(S)}] = [\phi_{ROH}] - [\phi_{Chl}] \tag{5}$$

In this equation the sign of $[\phi_{Chl}]$ is chosen arbitrarily. If the mol fractions in the hemiacetal mixture are designated X_R and X_S, respectively, the molecular rotation for the hemiacetal mixture $[\phi_{Ha}]$ can be expressed as (6).

$$[\phi_{Ha}] = X_R[\phi_{Ha(R)}] + X_S[\phi_{Ha(S)}] \tag{6}$$

By inserting (5) into (6) and using $X_R + X_S = 1$ eqn. (7) was obtained

$$[\phi_{Ha}] = [\phi_{ROH}] + [\phi_{Chl}] \, (2X_R - 1) \tag{7}$$

And by differentiation eqn. (7) was transformed to eqn. (8)

$$\mathrm{d}[\phi_{Ha}]/\mathrm{d}t = 2[\phi_{Chl}] \, \mathrm{d}X_R/\mathrm{d}t \tag{8}$$

Eqn. (8) shows that the change in $[\phi_{Ha}]$ with time is proportional to an equivalent change in X_R. By plotting $[\phi_{Ha}]$ *versus* X_A straight lines are obtained; X_A is the mol fraction of the epimer with the most shielded H_x-proton (eqn. (2)) which is determined by ^{1}H NMR-spectroscopy. From these lines (ϕ_{ROH}] and $[\phi_{Chl}]$ can be determined. This has been done for 3-methyl-2-butanol, 3,3-dimethyl-2-butanol and 1-cyclohexylethanol, Figs. 2a, b, and c and Table 1. The difference in $[\phi_{Chl}]_{364}{}^{25}$ for these alcohols can either be due to experimental
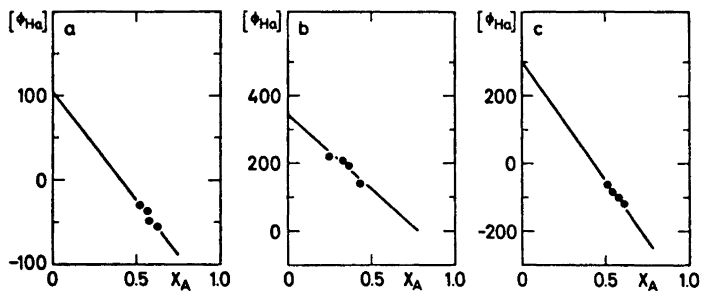

Fig. 2a, b, and c. A plot of the molecular rotation of the hemiacetal mixture $[\phi_{Ha}]$ at 25°C and 364 mμ in CCl$_4$, *versus* X_A. a: 3-methyl-2-butanol. b: 3,3-dimethyl-2-butanol. c: 1-cyclohexylethanol.

Table 1. Determination of the molecular rotations, $[\phi_{Chl}]$ and $[\phi_{ROH}]$, together with the molecular rotations of the alcohols used at 25°C and 364 mμ in CCl$_4$. $[\phi_{Chl}]$ and $[\phi_{ROH}]$ are calculated for 100 % optical purity.[22]

Name of alcohol	$(M_{ROH})_{364}{}^{25}$	Optical purity %	$[\phi_{Chl}]_{364}{}^{25}$	$[\phi_{ROH}]_{364}{}^{25}$
3-Methyl-2-butanol	− 6.70	55.3	244	− 36
3,3-Dimethyl-2-butanol	13.48	58.2	360	206
1-Cyclohexylethanol	− 14.74	68.5	336	− 83

uncertainty (the chemical shift difference of the two H_x-protons on a 60 MHz spectrometer is only about 0.5 Hz introducing a significant error into the mol fraction determinations) or else to vicinal interactions in the hemiacetal.

(c) The third observation [14] which showed that the mutarotation was due to epimerization was made by ^{1}H NMR-spectroscopy. The ^{1}H NMR-spectra showed that the signal from the methine proton, H_x (2), of the chloral hemiacetal of the sterically hindered 3,3-dimethyl-2-butanol appeared as two closely spaced singlets at 4.0 ζ. The mol fraction, X_A, of the most shielded H_x-proton (called H_a), changed from 0.72 to 0.50 in 1400 min. After that time no further change was observed. On the other hand, the chloral concentration was already constant after 10 min.[14]

The existence of the two diastereomeric hemiacetals is further demonstrated by the gas chromatogram of their acetyl derivatives, Fig. 3. The H_x-
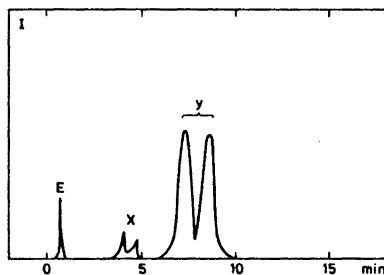

Fig. 3. Gas chromatogram of acetylated chloral hemiacetal of 2-butanol. E, X, and Y refer to diethylether, unreacted alcohol or hemiacetal, and the two diastereomeric acetylated hemiacetals, respectively.

protons in these isomers also show different chemical shifts in the ^{1}H NMR-spectrum. The two fractions were identified by their ^{1}H NMR-spectra and the superimposed spectra were identical to the spectrum of the mixture.

Based on kinetic investigations [5,15–17] the reaction mechanisms in Figs. 4 and 5 were proposed. The observed epimerization led us to believe that the reaction complex, Chl$\cdots$HA$\cdots$ROH was cyclic. In a cyclic reaction complex it may be possible to establish steric correspondence (asymmetric induction) between the prochiral carbon atom in chloral and the groups L, M, and S (1) in the alcohols. In the catalyzed reaction the ring closure of Chl$\cdots$HA$\cdots$ROH may give rise to at least four different transition states A, B, C, and D (see Fig. 4). But strong steric interactions between the very bulky trichlormethyl group and even the smallest group, S, make reaction complexes C and D very improbable, and their contributions to hemiacetal formation are therefore considered negligible compared to the contributions from A and B. In B the most bulky group, L, is placed nearer the ring atoms than in A, so that A is considered to be more stable. Therefore the initial rate of hemiacetal formation through A is higher than through B. In the uncatalyzed reaction, (Fig. 5), cyclic structures for the following reaction complexes $(Chl)_2\cdots(ROH)_2$ and $(Chl)_2\cdots(ROH)_3$ were proposed,[15,16] (Figs. 6a and b). Similar structures were proposed by Bell.[18]

The hemiacetals of the two optically active alcohols $C_6H_5CHOHCH_3$ and $CH_3CHOHCOOC_2H_5$ exhibited an anomalous epimerization [2] *i.e.* the

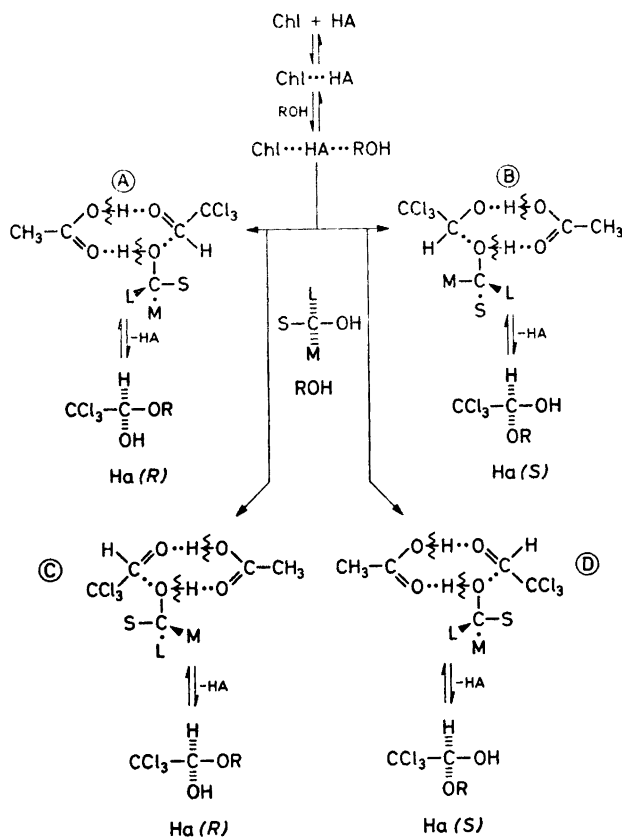*Fig. 4.* Possible reaction paths in the catalyzed formation of the chloral hemiacetals showing the cyclic structure of Chl$\cdots$HA$\cdots$ROH.
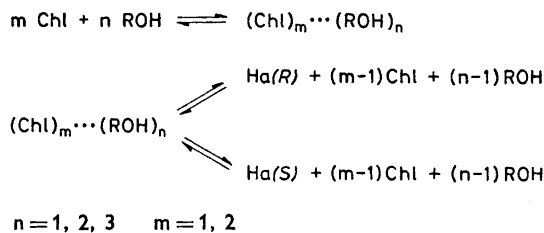

Fig. 5. Possible reaction path in the uncatalyzed formation of the chloral hemiacetals.

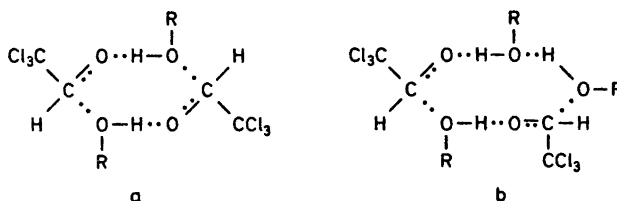*Fig. 6a and b.* Possible models of two cyclic reaction complexes $(Chl)_2 \cdots (ROH)_3$ and $(Chl)_2 \cdots (ROH)_3$.

sign of $d[\phi_{Ha}]/dt$ was opposite of that predicted by purely steric considerations. In these two examples, the most bulky group is polar, and the anomaly could be explained by assuming an attraction between the polar group and the trichloromethyl group in the cyclic reaction complexes considered. In this case, the formation of C and D would be favored compared with the formation of A and B. D, due to a steric effect (now a second order effect) is more stable than C, and the direction of the epimerization will be opposite of that predicted from purely steric reasons. This idea was further supported by the fact that the epimerization of optically active 1-cyclohexylethanol proceeded in a normal way. Further considerations regarding anomalous epimerizations will be reported later in this paper.

In previous papers [1-4] the mutarotation was used to predict configurations of alcohols without polar radicals. In order to examine the limits of the rule the following questions were considered.

(a) How large can the distance between the asymmetric center and the carbon atom carrying the oxygen atom be, or, in terms of the formula $L,M,SC(CH_2)_nOH$ (1), what is the maximum size of n which can still give rise to an observable mutarotation? This question has been answered by investigations of optically active alcohols, $CH_3CH_2CH(CH_3)(CH_2)_nOH$ with $n = 1$, 2, and 3. Only the alcohol with $n = 1$ gives rise to an observable mutarotation (Table 2).

Table 2. Predicted and observed sign of $d[\phi_{Ha}]/dt$ of the chloral hemiacetals of optically active primary alcohols of the following type $CH_3CH_2CH(CH_3)(CH_2)_nOH$.[3]

| Name of alcohol | Relative bulk | | | $(CH_2)_n$ n | Sequence | Sign $d[\phi_{Ha}]/dt$ | | Ref. |
	L	M	S			Predicted	Observed	
(S)-2-Methyl-1-butanol	CH_2CH_3	CH_3	H	1	L←M←S	positive	positive	19
(S)-2-Methyl-1-pentanol	CH_2CH_3	CH_3	H	2	L←M←S	positive	undeterminable	20,21
(S)-2-Methyl-1-hexanol	CH_2CH_3	CH_3	H	3	L←M←S	positive	undeterminable	20,21

(b) How large does the difference between L and M have to be in order to produce an observable mutarotation? In this connection optically active straight chain secondary alcohols have been investigated, Table 3. As expected no mutarotation is observed for optically active 4-octanol.

Table 3. Predicted and observed sign of $d[\phi_{Ha}]/dt$ of the chloral hemiacetals of straight chain secondary optically active alcohols of the following type L-CHOH-M.[3]

Name of alcohol	Relative bulk			Sequence	Sign of $d[\phi_{Ha}]/dt$		Ref.
	L	M	S		Predicted	Observed	
(S)-2-Butanol	CH_3CH_2	CH_3	H	L←M←S	positive	positive	22
(S)-3-Hexanol	$CH_3(CH_2)_2$	CH_3CH_2	H	L←M←S	positive	positive	22
(S)-4-Octanol	$CH_3(CH_2)_3$	$CH_3(CH_2)_2$	H	L←M←S	positive	undeter-minable	23

ANOMALOUS EPIMERIZATIONS

The observed sign of $d[\phi_{Ha}]/dt$ for alcohols containing polar groups such as phenyl and COOR groups is opposite of that predicted on the basis of purely steric considerations. This section concerns investigations of such cases which we call "anomalous epimerizations". The investigations are divided into four parts, noted a, b, c, and d.

a. Esters of optically active lactic acid and β-hydroxybutyric acid. In this part chloral hemiacetals of optically active lactates (9a) and β-hydroxybutyrates (9b) are treated.
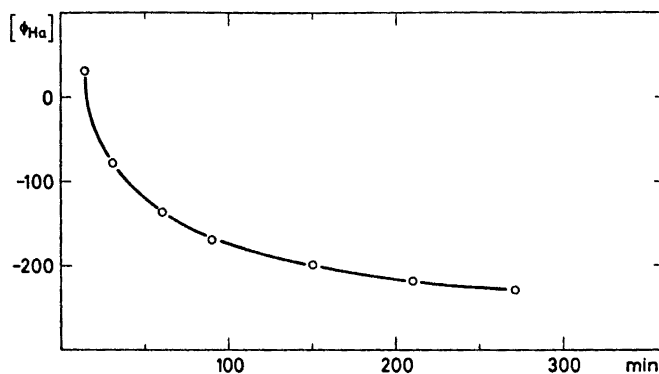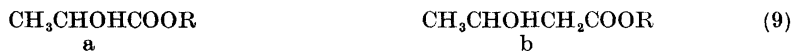
$$CH_3CHOHCOOR \qquad\qquad CH_3CHOHCH_2COOR \qquad (9)$$
$$a \qquad\qquad\qquad\qquad b$$

Fig. 7. A $[\phi_{Ha}],t$ curve of the chloral hemiacetal of (S)-ethyl lactate.

Table 4. Predicted and observed sign of $d[\phi_{Ha}]/dt$ of the chloral hemiacetals of esters of optically active lactic acid and β-hydroxybutyric acid.

Name of alcohol	Relative bulk			Sequence	Sign of $d[\phi_{Ha}]/dt$		Ref.
	L	M	S		Predicted	Observed	
(S)-Methyl lactate	COOCH$_3$	CH$_3$	H	L←M←S	positive	negative	24,25
(S)-Ethyl lactate	COOC$_2$H$_5$	CH$_3$	H	L←M←S	positive	negative	24,25
(S)-Butyl lactate	COOC$_4$H$_9$	CH$_3$	H	L←M←S	positive	negative	24,25
(S)-tert-Butyl lactate	COOC(CH$_3$)$_3$	CH$_3$	H	L←M←S	positive	negative	24,25
(S)-1-Ethylpropyl lactate	COOCH(C$_2$H$_5$)$_2$	CH$_3$	H	L←M←S	positive	negative	24,25
(S)-Neopentyl lactate	COOCH$_2$C(CH$_3$)$_3$	CH$_3$	H	L←M←S	positive	negative	24,25
(S)-Ethyl β-hydroxy-butyrate	CH$_2$COOC$_2$H$_5$	CH$_3$	H	L←M←S	positive	negative	26
(R)-Methyl β-hydroxybutyrate	CH$_2$COOCH$_3$	CH$_3$	H	L→M→S	negative	positive	26

Table 4 shows the relative bulk of the groups surrounding the asymmetric center, the sequence of L, M, and S, and the predicted and observed sign of $d[\phi_{Ha}]/dt$. The curve in Fig. 7 shows the course of $[\phi_{Ha}]$ *versus* time for chloral hemiacetal of (S)-ethyl lactate. This curve is representative of the other optically active esters considered in this part. It can be seen from Table 4 that in all cases the predicted and observed sign of $d[\phi_{Ha}]/dt$ are opposite, even when R is a bulky group such as *tert*-butyl or neopentyl. As mentioned before the anomaly may be explained by an interaction between the trichloromethyl group and the polar COOR group. This favors the formation of reac-

Table 5. Time dependence of the ^{1}H NMR-signals of the chloral hemiacetal of ethyl β-hydroxybutyrate.[a]

Time (min)	The mol fraction determined at	
	291Hz	298Hz
62	0.58	0.42
180	0.59	0.41
2440	0.67	0.33
4880	0.67	0.33

[a] These spectra were recorded at 60 MHz with a sweep-width of 500 Hz at 25°C in CCl$_4$. The initial concentrations of chloral and ethyl β-hydroxybutyrate were both 5×10^{-1} M.

tion complex D, in Fig. 4, and gives rise to the opposite direction of mutarotation than that predicted from steric considerations. By following the epimerization of the chloral hemiacetal of ethyl β-hydroxybutyrate in CCl_4 by ^{1}H NMR-spectroscopy (Table 5) it is observed that the difference in chemical shifts of the methine protons, H_x, of the diastereomeric hemiacetals is considerably larger (7 – 8 Hz) than that observed for hemiacetals of 3,3-dimethyl-2-butanol (0.5 Hz). Table 5 shows further that the mol fraction X_A of the most shielded methine proton, H_a, increases with time in contrast to the course of the epimerization of 3,3-dimethyl-2-butanol for which X_A decreases with time. At equilibrium, X_A is found to be about 0.5 Hz for chloral hemiacetals of alcohols containing no polar groups which means that the free energy of the two diastereomers are nearly equal. For hemiacetals of β-hydroxybutyrates the X_A-value at equilibrium is found to be higher than 0.5, which means that the free energy of the diastereomers are appreciably different. This is understandable due to the ease by which hydroxy acid esters can form different ring systems by hydrogen bonding in an intra- or intermolecular manner. The free energy of such rings formed from the two diastereomeric hemiacetals therefore may be different.

b. Alcohols containing aromatic and unsaturated radicals. This part concerns alcohols containing C_6H_5, $C_6H_5CH_2$, $CH_2=CH$, $CH_2=CHCH_2$, and *trans* $CH_3CH=CH$ groups. Figs. 8a and b show the course of $[\phi_{Ha}]$ *versus* time for

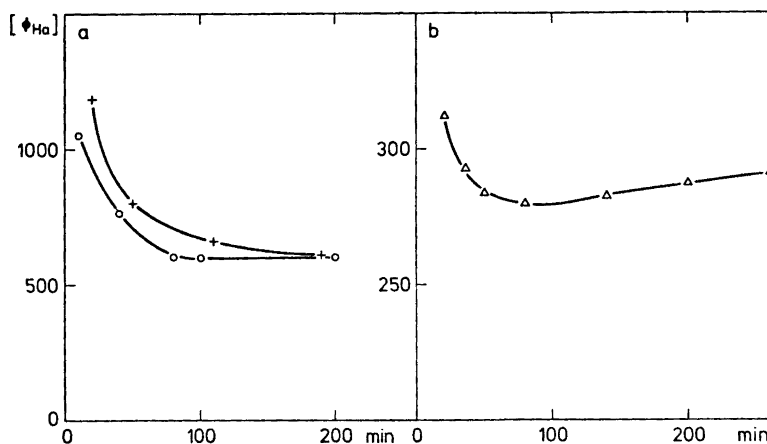*Fig. 8a and b.* The $[\phi_{Ha}],t$ curves of the chloral hemiacetals of (a) $+$: (S)-1-phenylethanol, O: (R)-cyclohexylphenylmethanol, and (b) $\triangle$: (S)-1-phenyl-2-propanol.

chloral hemiacetals of (S)-1-phenylethanol, (S)-1-phenyl-2-propanol, and (R)-cyclohexylphenylmethanol, and Figs. 9a and b show the corresponding course for (S)-3-buten-2-ol, (S)-*trans*-3-penten-2-ol, and (R)-4-penten-2-ol. The sign of $d[\phi_{Ha}]/dt$ for the above chloral hemiacetals is listed in Table 6, and in Table 7 the results of ^{1}H NMR-investigations are listed. Table 6 shows that the sign of $d[\phi_{Ha}]/dt$ for all the hemiacetals with the exception of those derived from (R)- and (S)-1-phenyl-2-propanol and (R)- and (S)-*trans*-3-
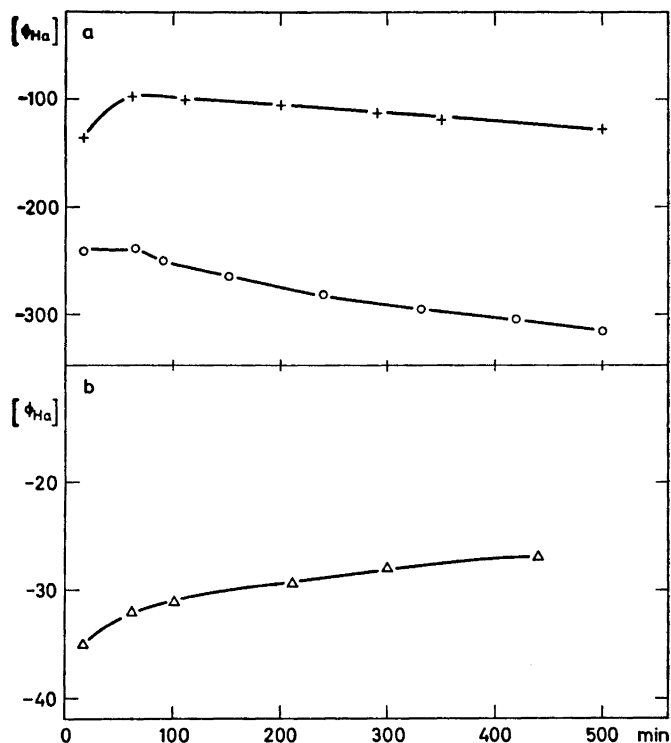
Fig. 9a and b. The $[\phi_{Ha}],t$ curves of the chloral hemiacetals of (a) $+$: (*S*)-3-buten-2-ol, O: (*S*)-*trans*-3-penten-2-ol, and (b) $\triangle$: (*S*)-4-penten-2-ol.

penten-2-ol is opposite of that predicted from steric considerations. The results thus indicate that phenyl and allyl groups give rise to an anomalous mutarotation whereas the benzyl group behaves normally. It is perhaps surprising that the vinyl group and the propenyl group do not behave in the same manner. Unfortunately in this case it seems as if the polar and the steric effects are both important, and, therefore, it is not possible to deduce any stereochemical rule for those alcohols with aromatic and unsaturated radicals.

The $[\phi_{Ha}],t$ curves of chloral hemiacetals of (*S*)-1-phenyl-2-propanol, (*S*)-3-buten-2-ol, and (*S*)-*trans*-3-penten-2-ol are not plain ones but contain a maximum or minimum. This unusual shape of a $[\phi_{Ha}],t$ curve can occur when more than one reaction contributes to the mutarotation. The sign of $d[\phi_{Ha}]/dt$ for those reactions which exhibit a maximum or minimum is that of the slope of the last part of the $[\phi_{Ha}],t$ curves; see part *d*. The ^{1}H NMR-investigations exhibit the same picture as described in section *a*, except for the chloral hemiacetal of 1-phenyl-2-propanol where no change in X_A (0.60) with time is observed. In addition X_A is smaller than 0.5 in the beginning of the reaction and higher at equilibrium for 1-phenylethanol and cyclohexylphenyl-

Table 6. Predicted and observed sign of $d[\phi_{Ha}]/dt$ of the chloral hemiacetals of optically active alcohols containing phenyl benzyl, vinyl, allyl, and crotyl radicals.

Name of alcohols	Relative bulk			Sequence	Sign of $d[\phi_{Ha}]/dt$		Ref.
	L	M	S		Predicted	Observed	
(R)-Cyclohexylphenylmethanol	C_6H_{11}	C_6H_5	H	L←M←S	positive	negative	27
(S) Cyclohexylphenylmethanol	C_6H_{11}	C_6H_5	H	L→M→S	negative	positive	27
(R)-1-Phenyl-2-propanol	$CH_2-C_6H_5$	CH_3	H	L→M→S	negative	negative	28
(S)-1-Phenyl-2-propanol	$CH_2-C_6H_5$	CH_3	H	L→M→S	positive	positive	28
(S)-1-Phenylethanol	C_6H_5	CH_3	H	L←M←S	positive	negative	24
(R)-1-Phenylethanol	C_6H_5	CH_3	H	L→M→S	negative	positive	24
(S)-3-Buten-2-ol	$CH=CH_2$	CH_3	H	L←M←S	positive	negative	29
(R)-3-Buten-2-ol	$CH=CH_2$	CH_3	H	L→M→S	negative	positive	29
(R)-4-Penten-2-ol	$CH_2CH=CH_2$	CH_3	H	L→M→S	negative	positive	23
(S)-4-Penten-2-ol	$CH_2CH=CH_2$	CH_3	H	L←M←S	positive	negative	23
(R)-trans-3-Penten-2-ol	$\overset{H}{}\!\!C=C\!<^{CH_3}_{H}$	CH_3	H	L→M→S	negative	negative	30
(S)-trans-3-Penten-2-ol	$\overset{H}{}\!\!C=C\!<^{CH_3}_{H}$	CH_3	H	L←M←S	positive	positive	30

methanol and perhaps also for the other alcohols in Table 7. This means that the most stable diastereomeric hemiacetals have the highest activation energy as illustrated in the energy profile in Fig. 1a.

c. Alcohols substituted with halogen atoms. The sign of $d[\phi_{Ha}]/dt$ for chloral hemiacetals of (R)-4-bromo-2-butanol and (S)-1-bromo-2-propanol are listed in Table 8. Only with the first mentioned hemiacetal is an effect of mutarotation obtained (Fig. 10). The second alcohol was too poorly resolved to give an observable effect. The $[\phi_{Ha}], t$ curve in Fig. 10 is a plain one.

d. The effect of solvents and initial concentrations on the mutarotation of (R)-4-methyl-2-pentanol. The curves in Fig. 11a and b and Fig. 12 show the course of $[\phi_{Ha}]$ *versus* time for the chloral hemiacetal of (R)-4-methyl-2-pentanol for different initial concentrations of chloral, alcohol, and acetic acid both in heptane and tetrachloromethane. The sign of $d[\phi_{Ha}]/dt$ was the same whether the solvent was heptane (Fig. 11) or CCl_4 (Fig. 12); even the equilibrium seems in both cases to fall into the same range. As seen from Fig. 11a and b the uncertainty of measurements in experiments with small concentrations excludes definite conclusions to be drawn from these data. The association mentioned in experiments with large concentrations of chloral,

Table 7. Time dependence of the ^{1}H NMR-signals of the methine protons in the chloral moiety in the two diastereomeric chloral hemiacetals of selected alcohols.[a]

1-Phenylethanol [b]			Cyclohexylphenyl-methanol [c]			3-Buten-2-ol [b]			4-Penten-2-ol [c]			3-Penten-2-ol [c]		
Time (min)	Mol fraction		Time (min)	Mol fraction		Time (min)	Mol fraction		Time (min)	Mol fraction		Time (min)	Mol fraction	
	271Hz	293Hz		270Hz	289Hz		285Hz	287Hz		286Hz	288Hz		286Hz	288Hz
30	0.33	0.67	28	0.42	0.58	10	0.50	0.50	75	0.53	0.47	32	0.56	0.44
40	0.37	0.63	58	0.44	0.56	46	0.58	0.42	124	0.53	0.47	45	0.58	0.42
74	0.39	0.61	94	0.49	0.51	65	0.62	0.38	167	0.52	0.48	60	0.60	0.40
86	0.41	0.59	130	0.52	0.48	105	0.63	0.37	1440	0.67	0.33	75	0.61	0.39
120	0.48	0.52	400	0.53	0.47	160	0.64	0.36				105	0.63	0.37
156	0.49	0.51	430	0.56	0.44	193	0.65	0.35				155	0.65	0.35
160	0.52	0.48	520	0.58	0.42	1440	0.70	0.30				233	0.66	0.34
1440	0.59	0.41	550	0.62	0.38							365	0.66	0.34
2880	0.68	0.32	654	0.63	0.37							1440	0.66	0.34
			1360	0.80	0.20									
			2800	0.80	0.20									

[a] These spectra were recorded at 60 MHz width a sweep-width of 500 Hz at 25°C in CCl_4.
[b] The initial concentrations of chloral and alcohol are both 5×10^{-1} M.
[c] The initial concentrations of chloral, alcohol, and acetic acid are 5×10^{-1} M, 5×10^{-1} M, and 5×10^{-3} M, respectively.

Table 8. Predicted and observed sign of $d[\phi_{Ha}]/dt$ of the chloral hemiacetals of optically active alcohols containing CH_2Br and CH_2CH_2Br groups.

Name of alcohol	Relative bulk			Sequence	Sign of $d[\phi_{Ha}]/dt$		Ref.
	L	M	S		Predicted	Observed	
(S)-1-Bromo-2-propanol	CH_2Br	CH_3	H	L←M←S	positive	undeterminable	26,28
(R)-4-Bromo-2-butanol	$(CH_2)_2Br$	CH_3	H	L→M→S	negative	positive	26,31

alcohol, and acetic acid sometimes gives rise to a maximum or a minimum in the first part of the $[\phi_{Ha}], t$ curve. Therefore using $[\phi_{Ha}], t$ curves in order to determine the absolute configuration of alcohols containing nonpolar groups it is recommended that the concentrations of chloral and alcohols are
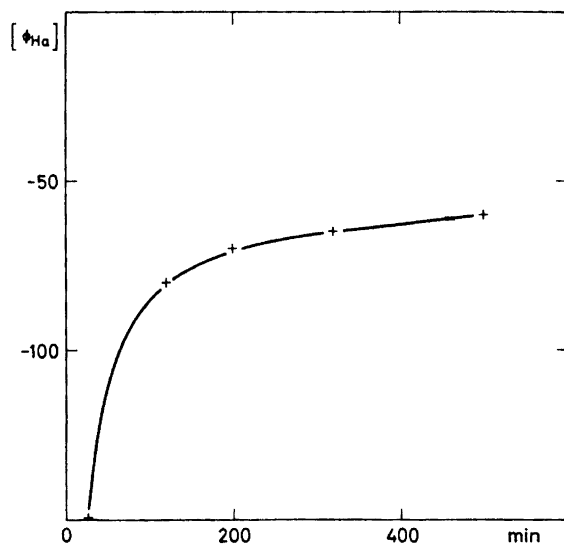
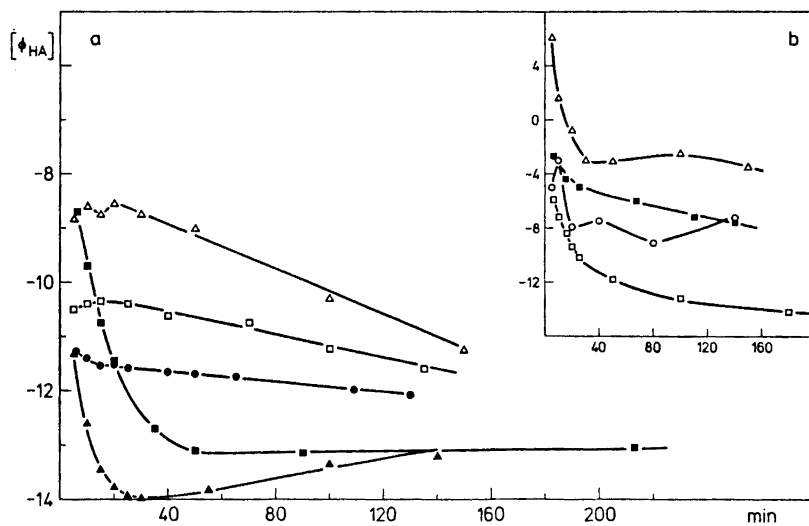*Fig. 10.* The $[\phi_{Ha}], t$ curve of the chloral hemiacetals of (R)-4-bromo-2-butanol.

Fig. 11a and b. The $[\phi_{Ha}], t$ curves of the chloral hemiacetal of (R)-4-methyl-2-pentanol in heptane at 25°C.

(a) △: $[Chl]_0 = [ROH]_0 = 1 \times 10^{-1}$ M and $[HAc] = 1 \times 10^{-3}$ M,
□: $[Chl]_0 = [ROH]_0 = 2 \times 10^{-1}$ M and $[HAc] = 2 \times 10^{-3}$ M,
●: $[Chl]_0 = [ROH]_0 = 2 \times 10^{-1}$ M,
■: $[Chl]_0 = [ROH]_0 = 2 \times 10^{-1}$ M and $[HAc] = 2 \times 10^{-2}$ M,
▲: $[Chl]_0 = [ROH]_0 = 2 \times 10^{-1}$ M and $[HAc] = 2 \times 10^{-1}$ M,
(b) △: $[Chl]_0 = [ROH]_0 = 2 \times 10^{-2}$ M,
■: $[Chl]_0 = [ROH]_0 = 2 \times 10^{-2}$ M and $[HAc] = 2 \times 10^{-3}$ M,
□: $[Chl]_0 = [ROH]_0 = 2 \times 10^{-2}$ M and $[HAc] = 2 \times 10^{-2}$ M,
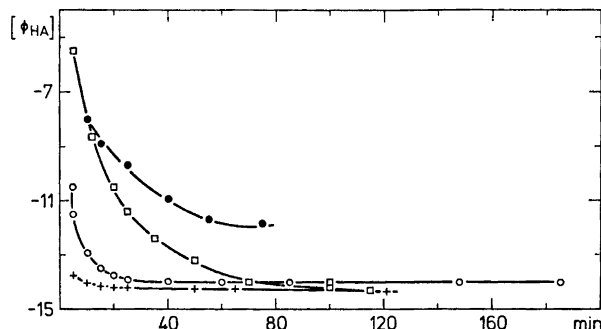○: $[Chl]_0 = [ROH]_0 = 5 \times 10^{-3}$ M and $[HAc] = 5 \times 10^{-3}$ M.

Fig. 12. The $[\phi_{Ha}],t$ curves of the chloral hemiacetals of (R)-4-methyl-2-pentanol in CCl_4 at 25°C.

O: $[Chl]_0 = [ROH]_0 = 2 \times 10^{-2}$ M,
●: $[Chl]_0 = [ROH]_0 = 2 \times 10^{-2}$ M and $[HAc] = 2 \times 10^{-2}$ M,
■: $[Chl]_0 = [ROH]_0 = 2 \times 10^{-2}$ M and $[HAc] = 2 \times 10^{-1}$ M,
+: $[Chl]_0 = [ROH]_0 = 2 \times 10^{-1}$ M and $[HAc] = 2 \times 10^{-3}$ M.

in the range between 1×10^{-1} M and 1×10^{-2} M and for acetic acid between 1×10^{-2} M and 2×10^{-4} M, and that the sign of $d[\phi_{Ha}]/dt$ refers to the slope of the last part of the curve.

EXPERIMENTAL

The UV-measurements were made on a Pye-Unicam-Philips spectrophotometer Model Sp 800. The NMR-spectra were recorded on a Varian A 60A spectrophotometer with TMS as an internal standard and the gaschromatograms on an analytical Perkin-Elmer Model F 21 and on a preparative Perkin-Elmer Model 141. The rotations were measured on a Perkin-Elmer polarimeter Model 141. The experimental conditions for the investigations of epimerization of the chloral hemiacetals are listed in Table 9 together with references to preparations and resolutions of the optically alcohols used.

Esters of (S)-*lactid acid.* Ethyl and butyl lactate were commercial products. Methyl lactate (b.p. 40 – 45°C/14 mmHg, yield 30 %) and *tert*-butyl lactate (b.p. 70 – 87°C/14 mmHg, yield 50 %) were prepared according to the literature.[25] Neopentyl lactate (b.p. 79 – 87°C/14 mmHg, yield 50 %) and 1-ethylpropyl lactate (b.p. 74 – 76°C/10 mmHg, yield 70 %) were prepared by analogy with the other esters. The identity of the esters was supported by NMR-spectra.

Esters of β-hydroxybutyric acid. The β-hydroxybutyric acid was resolved as reported[32] and yielded 45 % of both of the enantiomers. The enantiomers were treated with ethanol and methanol to prepare ethyl β-hydroxybutyrate (b.p. 76 – 78°C/14 mmHg, yield 34 %)[33] and the methyl ester (b.p. 65 – 66°C/15 mmHg, yield 20 %), respectively.

(S)-*3-methyl-1-pentanol and* (S)-*4-methyl-1-hexanol.* Reaction of paraformaldehyde[36] and ethylene oxide[37] with (S)-2-methyl-1-butyl magnesium bromide gave (S)-3-methyl-1-pentanol (b.p. 52 – 57°C/12 mmHg, yield 50 %) and (S)-4-methyl-1-hexanol (b.p. 70 – 73°C/11 mmHg, yield 65 %), respectively. (S)-1-Bromo-2-methylbutane was prepared from (S)-2-methyl-1-butanol and phosphorus tribromide.[35]

The enantiomers of the following seven alcohols were prepared by optical resolution of the brucine or chinchonidine salts of their hydrogen phthalates.[49]

(R)- *and* (S)-*4-octanol* (b.p. 70 – 71°C/11 mmHg, yield 20 %).[38,39]

(R)- *and* (S)-*cyclohexylphenylmethanol* (m.p. 66 – 68°C, recrystallized from ligroin, yield 20 %)[40] was prepared by a Grignard synthesis from cyclohexyl chloride and benzaldehyde.[41]

Table 9. The experimental conditions for the investigations of the epimerizations of chloral hemiacetals. All these epimerizations were carried out in heptane solution at 25°C.

Name of alcohol	Initial concentrations			$[\phi]_{364}^{25}$ of the alcohols	Optical [a] purity of the alcohols	Synthe-ses of the alco-hols, lit.
	ROH (mol/l)	Chl (mol/l)	HA (mol/l)			
(S)-Methyl lactate	10^{-1}	10^{-1}	10^{-3}	$+10.6°$	43 %	25
(S)-Ethyl lactate	10^{-1}	10^{-1}	10^{-3}	$-7.43°$	87 %	25
(S)-Butyl lactate	10^{-1}	10^{-1}	10^{-3}	$-33.0°$		
(S)-tert-Butyl lactate	10^{-1}	10^{-1}	10^{-3}	$-4.04°$	30 %	25
(S)-1-Ethylpropyl lactate	10^{-1}	10^{-1}	10^{-3}	$-6.10°$		25
(S)-Neopentyl lactate	10^{-1}	10^{-1}	10^{-3}	$-55.6°$		25
(S)-Ethyl β-hydroxybutyrate	10^{-1}	10^{-1}	10^{-3}	$+11.5°$	30 %	32,33
(R)-Methyl β-hydroxy-butyrate	10^{-1}	10^{-1}	10^{-3}	$-17.2°$	43 %	32,34
(S)-3-Methyl-1-pentanol	10^{-1}	10^{-1}	2×10^{-4}	$+20.4°$	77 %	35,36
(S)-4-Methyl-1-hexanol	10^{-1}	10^{-1}	2×10^{-4}	$+19.6°$		35,37
(S)-4-Octanol	10^{-1}	10^{-1}	10^{-3}	$+0.24°$	19 %	38,39
(R)-Cyclohexylphenyl-methanol [b]	10^{-1}	10^{-1}	2×10^{-4}	$+92.8°$	57 %	40,41
(S)-Cyclohexylphenyl-methanol [b]	10^{-1}	10^{-1}	2×10^{-4}	$-171°$	90 %	40,41
(R)-1-Phenyl-2-propanol	10^{-1}	10^{-1}	2×10^{-4}	$-116°$	70 %	42
(S)-1-Phenyl-2-propanol	10^{-1}	10^{-1}	2×10^{-4}	$+174°$	100 %	42
(S)-1-Phenylethanol	5×10^{-2}	5×10^{-2}	2×10^{-4}	$-159°$		43,44
(R)-1-Phenylethanol	5×10^{-2}	5×10^{-2}	10^{-4}	$+94°$		43,44
(S)-3-Buten-2-ol	10^{-1}	10^{-1}	10^{-3}	$+43.8°$	35 %	45
(R)-3-Buten-2-ol	10^{-1}	10^{-1}	10^{-3}	$-7.21°$	9 %	45
(R)-4-Penten-2-ol	10^{-1}	10^{-1}	10^{-3}	$-11.3°$	52 %	46
(S)-4-Penten-2-ol	10^{-1}	10^{-1}	10^{-3}	$+21.0°$	94 %	46
(R)-trans-3-Penten-2-ol	5×10^{-2}	5×10^{-2}	10^{-3}	$-5.9°$		47
(S)-trans-3-Penten-2-ol	10^{-1}	10^{-1}	10^{-3}			47
(S)-1-Bromo-2-propanol	10^{-1}	10^{-1}	10^{-3}	$+0.12°$	2 %	48
(R)-4-Bromo-2-butanol	10^{-1}	10^{-1}	10^{-3}	$-0.61°$	2.4 %	48

[a] The optical purity is the percentage of the measured rotation in relation to the maximum rotation referred to in lit.

[b] The mutarotation of chloral hemiacetals of these alcohols have also been investigated in cyclohexane at 589 mμ.

(R)- and (S)-*1-phenyl-2-propanol* (b.p. 94 − 96°C/13 mmHg, yield 30 %).[42]
(R)- and (S)-*1-phenylethanol* (b.p. 93 − 93.5°C/13 mmHg, yield 15 %).[43,44]
(R)- and (S)-*3-buten-2-ol* (b.p. 96 − 98°C, yield 10 %).[45]
(R)- and (S)-*4-penten-2-ol* (b.p. 114 − 116°C, yield 40 %).[46]
(R)- and (S)-*3-penten-2-ol* [47] were resolved from a commercial product (b.p. 120 − 121°C, yield 20 %). The alcohols were further purified by preparative gas chromatography (poly-1,4-butandiol succinate column, column temp. 90°C, injection temp. 175°C, N_2 flow 35 ml/min). The main peak was detected after 3 − 4 min. The product was identified by its ¹H NMR-spectrum as the *trans*-alcohol.

(S)-*1-Bromo-2-propanol and* (R)-*4-bromo-2-butanol.* Resolution of these alcohols was attempted by preferential acetylation of one enantiomer in the presence of brucine in a manner analogous to that used for partial resolution of *erythro*-3-bromo-2-butanol.[48] This method proved to be unsatisfactory as the low optical purity in Table 9 shows.

Acetyl-2-butanol chloral hemiacetal. This compound was made as reported [50] from 2-butanol chloral hemiacetal mixture and acetyl chloride and pyridine in ether (b.p. 104 − 106°C/12 mmHg, yield 70 %). The separation of the two isomers was carried out by gas chromatography, Fig 3 (poly-1,4-butandiol succinate column, column temp. 120°C, injection temp. 250°C, and N_2 flow 33 ml/min).

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